REMARKS

This is in response to the Office Action mailed on September 26, 2007.

Claims 35 and 36 have been added. Accordingly, claims 2, 4, 8-10, 24-35 and 36 are now pending in the application.

Support for the subject matter of new claims 35 and 36, relating peptides with 8 to 75 amino acids, can be found throughout the application and claims as originally filed, for example, at page 7, lines 16-23 and in Example 2.

Applicant submits that no new matter has been added to the application.

§112 Enablement Rejection of the Claims

Claims 2, 4, 8-10, 24-33 and 34 were rejected under 35 U.S.C. § 112, first paragraph, as allegedly lacking enablement. The Examiner essentially makes four allegations. First, the Examiner alleges that the specification provides insufficient evidence of cell surface presentation of peptides to generate an immune response, or cytotoxic T cell mediated killing. Second, the Examiner reiterates that there are factors that need to be considered that are not disclosed by the specification (e.g., cell death caused by photochemical treatment). Third, the Examiner states that there is insufficient evidence that the claimed methods would generate activated cytotoxic T cells to enable cell killing. Fourth, the Examiner maintains that MHC I is down-regulated in cancer cells.

The test for enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation. *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 231 U.S.P.Q. 81, 94 (Fed. Cir. 1986), cert. denied, 480 U.S. 947 (1987).

Claim 2 is directed to a method of presenting an antigenic peptide on the surface of a viable cancer cell, said method comprising: contacting said cancer cell with said antigenic peptide and with a photosensitizing agent, wherein said peptide and said agent are each taken up into an intracellular membrane-restricted compartment of said cell; irradiating said cell with light of a wavelength effective to activate the photosensitizing agent, such that the membrane of said intracellular compartment is disrupted, releasing

said peptide into the cytosol of the cell, without killing the cell; wherein, said released antigenic peptide, or a part thereof of sufficient size to generate a cytotoxic T cell response, is subsequently presented on the surface of said cell by a class I MHC molecule; wherein presentation of the antigenic peptide, or part thereof, on the surface of said cell results in cytotoxic T cell mediated cell killing; and wherein the photosensitizing agent is selected from the group consisting of a porphyrin, phthalocyanine and a chlorin.

Claim 24 is directed to a method of presenting an antigenic peptide or a part thereof on the surface of a viable antigen presenting cell, said method comprising: contacting said cell with the antigenic peptide and with a photosensitizing agent, wherein said peptide and said agent are each taken up into an intracellular membrane-restricted compartment of said cell; irradiating said cell with light of a wavelength effective to activate the photosensitizing agent, such that the membrane of said intracellular compartment is disrupted, releasing said peptide into the cytosol of the cell, without killing the cell; wherein, said released peptide, or a part thereof of sufficient size to generate an immune response, is subsequently presented on the surface of said cell by a class I or II MHC molecule; wherein presentation of the peptide, or part thereof, on the surface of said cell results in stimulation of an immune response; and wherein the photosensitizing agent is selected from the group consisting of a meso-tetraphenylporphine with 4 sulfonate groups ($TPPS_4$), meso-tetraphenylporphine with 2 sulfonate groups on adjacent phenyl rings ($TPPS_{2a}$), or aluminum phthalocyanine with 2 sulfonate groups on adjacent phenyl rings ($AlPcS_{2a}$).

The issues raised by the Examiner are addressed separately below.

Cell-Surface Presentation

The Examiner admits that most cells express MHC class I molecules, that MHC class II molecules are found on antigen presenting cells and that the present photochemical methods can be used to internalize exogenous molecules (see Office Action last 3 lines of page 2, and page 3, lines 3-6 of last paragraph (Jan. 9, 2007)). Yet, the Examiner expresses doubt that the specification enables presentation of peptide antigens on cell surfaces.

Applicant submits that when a foreign peptide is internalized into a cell, the data provided in the specification *proves* that the peptide will be presented on the surface of the cell.

Applicant has provided data showing that cell killing by cytotoxic T cells occurs only when the cytotoxic T cell recognizes the antigenic peptide on the surface of a cell. These data also demonstrate that methods of the invention achieve presentation of sufficient antigenic peptide to allow recognition and cytotoxic T cell mediated cell killing. In particular, Example 2 describes FM3 melanoma cells that were treated with the $AlPcS_{2a}$ photosensitizer for 18 hours, then loaded with chromium and incubated with the MART-1 peptide for 5 hours. The chromium is taken up into the cells and used as a marker for cell lysis. After chromium uptake and incubation with the MART-1 peptide, the cells are washed to remove residual peptide, chromium, etc. Then, the cells are exposed to light (as indicated in FIG. 3). The cells are then incubated for eighteen hours to allow internalization and display of the MART-1 peptide on the FM3 melanoma cells. After this incubation, the melanoma cells are exposed for four hours to cytotoxic T cells that were specific for the MART-1 peptide, and then the amount of chromium released into the medium was measured as a marker of cell lysis. FIG. 3 shows that the percent cytotoxicity increases with increasing time of light exposure. When no light is used so that little or no photo-internalization of the MART-1 peptide occurs, little cell death is observed. However, increased light exposure leads to increased uptake and display of the MART-1 peptide which then leads to increased killing by the cytotoxic T cells.

These results mean that the MART-1 peptide is internalized and then presented on the cell's surface by Applicant's methods and the cytotoxic T cells then kill those cells that display the MART-1 peptide. No other conclusion can be drawn from this evidence. The Examiner has previously agreed and stipulated that Example 2 is enabled (Oct. 24, 2003 Office Action at page 2; Aug. 23, 2004 Office Action at page 4; April 1, 2005 Office Action at page 3). Accordingly, one of skill in the art would definitively conclude that Example 2 demonstrates cell surface display of sufficient antigenic peptide to result in cytotoxic T cell mediated cell killing.

Moreover, the specification explains exactly how to practice the subject matter of claims 2 and 24 so that antigenic peptides can be presented on cell surfaces. In particular, page 8 refers to cancer vaccines which stimulate cytotoxic T-lymphocytes. Pages 9-10 recite that cytotoxic cells are stimulated by presentation of foreign antigens by antigen-presenting cells via the MHC molecules. A CTL clone is then formed and the target cell and other target cells with the same peptide-MHC complex can then be killed by the CTL clone. The present invention is concerned with both the generation of the CTL clone and also the CTL mediated death. Claim 24 is directed to the generation of a clone in which antigen presenting cells take up the peptide of interest by PCI which is then expressed and CTL activation achieved. Claim 2 covers the action of the primed CTL clone on cells expressing the peptide by PCI. As discussed further herein, it is quite common for CTLs reactive to tumor antigens to be inherently present in cancer patients, or such CTL may be generated by vaccination, without those CTLs being able to attack the cancer cells. PCI treatment of the cancer cells is proposed to allow those CTL to unleash that attack.

Applicant submits that the Examiner has failed to recognize compelling evidence of enablement that Applicant has repeatedly provided. Moreover, although Applicant's evidence is compelling, the evidence provided by applicant need not even be conclusive but merely convincing to one skilled in the art. M.P.E.P. § 2164.05.

Moreover, Applicant reminds the Examiner that,

> The test [for undue experimentation] is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed to enable the determination of how to practice a desired embodiment of the claimed invention.

PPG Indus., Inc. v. Guardian Indus. Corp., 75 F.3d 1558, 1564, 37 USPQ2d 1618, 1623 (Fed. Cir. 1996). Thus, even if some experimentation is needed the invention is still enabled.

Applicant submits that one of skill in the art would definitively conclude that the specification enables cell surface presentation of antigenic peptides.

Photochemical-Induced Cell Death

The Examiner alleges that factors critical to the claimed method were not adequately described in the specification at the time of filing and that a post-filing Declaration cannot be used to cure any alleged defects. The Declaration is not provided as the source of missing information on the invention, but rather as evidence to illustrate that the teachings of the specification are accurate and to show that the results obtained are not unpredictable.

The alleged defects in the specification were addressed in Applicant's submissions as far back as August 11, 2003 (see page 9 of Applicant's Aug. 11, 2003 response). Optimization of the photochemical internalization technique to avoid cell death, and thereby toxicity from this effect is readily achievable. This is shown in Applicant's specification, for example, at page 18, line 27 to page 20, line 6, where cells were maintained alive for several days (e.g., 7 days) after photochemical internalization of a variety of molecules. Similarly, Example 4 shows that photochemical internalization of plasmid encoding green fluorescent protein yields cells that are healthy and fully capable of expressing the green fluorescent protein.

The present specification further discloses how to avoid unnecessary cell death. On page 14, the specification discloses that the potency of the photosensitizing agent, and its ability to disrupt membranes on irradiation should be taken into account (lines 9-14). Page 14 of the specification also discloses that the light irradiation step should be appropriately selected so that it does not deleteriously affect the viability and functionality of the cells (lines 14-27). Moreover, the proportion of cells that should be maintained in a live state are provided on page 14, from lines 28 to 33. The specification also teaches that when exposing cells to light care should be taken because some cells may receive more light than others (page 14, line 34 to page 15, line 18). Furthermore, on page 15 it is explicitly taught that the methods may be modified to regulate the proportion of surviving cells by selection of appropriate light dosages and photosensitivity agents (lines 19-23). Thus the specification clearly teaches how toxicity, which may result from the PCI method, should be avoided.

With regard to the molecule to be introduced, the present claims are directed to antigenic peptides - not toxins. The specification describes appropriate peptides that may be used (see, e.g., page 7, line 33 to page 8, line 30). Moreover, internalization of toxic molecules would defeat the purpose of the claimed invention because such toxic molecules would kill the cells so that no cell surface presentation could take place. Thus, as expressed plainly in the claims, the cells are live cells that present antigenic peptides on their cell surfaces - use of toxic molecules is not part of the invention.

If a peptide was observed to have a toxic property this would be immediately apparent in an *in vitro* test and one of skill in the art would understand that this peptide was not appropriate for cell surface presentation (and moreover was not part of the invention). As mentioned above the specification teaches that one should ensure that cell viability is maintained and indeed this is a requirement of the claims. If cell viability were found to be impaired this would immediately indicate that the molecule being internalized was toxic and could hence be avoided.

Thus, the specification clearly does teach one of skill in the art how to optimize the methods of the invention so that a variety of non-toxic peptides, photochemical internalization agents and the appropriate light exposure times can readily be employed.

Generation of Cytotoxic T Cells (CTLs)

The Examiner alleges that the claimed methods do not enable generation of cytotoxic T cells, therefore dismissing the relevance of Example 2 which shows CTL mediated cell killing of melanoma cells. Thus, the Examiner states with respect to Example 2: "the example is not representative of the generation of cytotoxic T cell killing which encompasses the generation of activated T cells from naïve T cells."

Applicant submits that the generation of primed CTLs is not necessary for performance of the invention and accordingly the present claims do not include a step for generating CTLs.

Instead, CTLs reactive with tumor antigens are inherently present. As support for this fact, Applicants enclose an article by Salgaller *et al.* (Cancer Research, 56: 4749-4757 (1996)). Salgaller *et al.* examined the effect of *in vivo* immunization with cancer

peptides in the PBMC of patients and the generation of a peptide specific CTL response was determined by interferon (IFN) secretion levels. PBMC samples from patients were taken before or after challenge with a particular cancer peptide (pre- or post-immune serum) and the PBMC samples were then further stimulated with relevant peptide *in vitro*. Thus, Salgaller et al. detected whether a CTL response was mounted in pre-immune and post-immune serum, which is indicative of primed CTLs.

Table 2 on page 4751 of the Salgaller et al. article illustrates stimulation with melanoma relevant peptides G9-209 and G9-209/2M. Note that even in pre-immune samples CTL responses were observed. Therefore, the patients already had CTL primed to the melanoma peptides. This is not surprising because CTLs reactive with tumor antigens are known to be inherently present in cancer patients.

Thus one can perform the method of claim 2 as set forth without the need to generate primed CTLs.

However, if one of skill in the art wished to generate primed CTLs, procedures are readily available in the art. This is evidenced by the enclosed article by Valmori (J. Immunol., 160: 1750-1758 (1998)), which illustrates that the production of primed CTLs by *in vitro* methods was known in the art at the time of the invention. (This article also notes that Melan-A-specific CTL are identified in patients that have not been immunized (see page 1750, right hand column, lines 3-5).) In this article PBMC are stimulated to produce Melan-A-specific CTL by using a Melan-A peptide.

Furthermore, primed CTL can be generated by immunization of individuals *in vivo*. Salgaller *et al* discloses *in vivo* immunization with relevant peptides to produce primed CTL, see e.g. Table 2 on page 4751. *In vivo* immunization (see second column) with the peptides of interest resulted in the generation of primed CTL to that peptide, see e.g. G9-209/2M immunization which lead to increased IFN production when exposed to G9-209/2M *in vitro* (column 5).

With regard to claim 24 which concerns antigen presenting cells, the Examiner has already maintained that APCs are enabled for use in the claimed method (see line 4 of the Official Action, page 6) since they are capable of generating an immune response.

Thus, the claims are clearly directed to subject matter that is enabled by the specification.

MHC I Regulation in Cancer Cells

The Examiner maintains that MHC-I down-regulation occurs in cancer cells because the Nijman *et al* article allegedly teaches that MHC I down-regulation can be an issue.

However, as reported in the specification and as will be appreciated by the Examiner, cancer vaccines are known in the art. Such vaccines work on the basis of stimulating CTL production such that those CTLs will attack tumour cells bearing the vaccine peptides. However, CTLs can only recognize and destroy cells presenting the antigenic peptide from the vaccine in the context of a class I MHC molecule. Thus it is evident from the emergence of cancer vaccines as useful therapeutic agents that even if some tumors might exhibit down-regulation of MHC class I molecules, this is not a universal phenomenon and MHC class I expression on cancer cells is sufficiently prevalent such that cancer vaccine development is appropriate.

Moreover, it is evident from the enclosed articles by Salgaller *et al* and Valmori *et al* that tumor-reactive CTL can be generated. These documents are specifically concerned with the development of CTL that will target tumour cells and these would only be useful if those tumour cells were still able to express antigens by the MHC class I mechanisms. For example in Figure 2 on page 4755 in Salgaller *et al*, the amount of lysis of a melanoma line 624.38 mel was analyzed (filled squares). Lysis was clearly achieved, thus demonstrating that appropriate MHC I expression was present to permit CTL targeting. Similarly, Figure 1 of Valmori *et al* on page 1752 shows that the Me melanoma cell lines all experienced cell lysis by CTL from tumour infiltrated lymph nodes. Thus, these cancer cells all express MHC class I sufficiently for antigen presentation and CTL recognition to occur.

Example 2 further illustrates that cancer cells (in that case melanoma cells) adequately express MHC class I to allow presentation of MART-1 peptide and its recognition by CTLs.

Thus the alleged down-regulation of MHC class I molecules does not constitute a bar to performance of the invention as the method can be carried out for the large number of cancers in which down-regulation is not observed.

With regard to claim 24, it will be noted that this claim is not limited to cancer cells and thus in addition concerns cells in which no MHC class I down regulation has been observed and to which this objection should not apply.

Applicant recognizes that in order to make a rejection, the examiner has the initial burden to establish a reasonable basis to question the enablement provided for the claimed invention. *In re Wright*, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993) (examiner must provide a reasonable explanation as to why the scope of protection provided by a claim is not adequately enabled by the disclosure). The Examiner has provided his reasons for making the rejection.

However, Applicant has also been responsive and has repeatedly provided evidence and data showing that the statements in Applicant's application are correct. A specification disclosure which contains a teaching of the manner and process of making and using an invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented *must* be taken as being in compliance with the enablement requirement of 35 U.S.C. 112, first paragraph, unless there is a reason to doubt the objective truth of the statements contained therein. See, MPEP § 2164.01. Here, there can be no doubt that the evidence is truthful – the data speak for themselves. Therefore, Applicant urges the examiner to look for enabled, allowable subject matter and communicate to applicant what that subject matter is as he is required to do under MPEP § 2164.01 at the earliest point possible in the prosecution of the application.

Withdrawal of this rejection of claims 2, 4, 8-10, 24-33 under 35 U.S.C. § 112, first paragraph, is respectfully requested.

§112 Written Description Rejection of the Claims

To satisfy the written description requirement, Applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he was in

possession of the invention, and that the invention, in that context, is whatever is now claimed. *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555 (Fed. Cir. 1991), and see M.P.E.P. § 2163.02.

Claim 30 has been rejected under 35 U.S.C. § 112, first paragraph, as allegedly lacking written description. The Examiner alleges that the specification and claims as filed do not provide support for a method employing a (i) sulfonated tetraphenylporphine, a (ii) disulfonated aluminum phthalocyanine or (iii) a tetrasulfonated aluminum phthalocyanine.

Applicant submits that the specification specifically describes all three of these subgenuses and provides several examples of photosensitizers falling within their scope. Thus, page 12, lines 17-19 recite: "di- and tetrasulfonated aluminum phthalocyanine, sulfonated tetraphenylporphines ($TPPS_n$)," and further state that these photosensitizing agents localize in endosomes and lysosomes (see page 12, lines 11-14 and lines 17-23). Thus, the specification literally supports the photosensitizers recited in claim 30.

Furthermore, examples from these groups of photosensitizers have been described and used in accordance with the invention. Preferred photosensitizing agents are stated to include $TPPS_4$, $TPPS_{2a}$ and $AlPcS_{2a}$ (see page 12, lines 32-34). These are respectively meso-tetraphenylporphine with 4 sulfonate groups, meso-tetraphenylporphine with 2 sulfonate groups and aluminum phthalocyanine with 2 sulfonate groups. The first two compounds are thus examples of group (i) (i.e. sulfonated tetraphenylporphines) and the final compound is an example of group (ii) (i.e. disulfonated aluminum phthalocyanine). These compounds are further described and used in the Examples, see e.g. page 18, from lines 9-13.

Thus not only are the groups claimed in claim 30 explicitly disclosed and exemplified in the specification (including three specific examples of those groups), but they have also been shown to be useful in accordance with methods of the invention.

Applicant submits that no new matter is present in claim 30, and respectfully requests withdrawal of this rejection of claim 30 under 35 U.S.C. § 112, first paragraph.

§102 Rejection of the Claims

Claims 2, 4, 8-10, 24-29, 30-33 and 34 were rejected under 35 U.S.C. § 102(b) as allegedly anticipated by PCT Application Publication No. WO96/07432 by Berg. The Examiner alleges that WO96/07432 inherently anticipates the invention.

A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference. *Verdegaal Bros. v. Union Oil of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). The identical invention must be shown in as complete detail as is contained in the claim. *Richardson v. Suzuki Motor Co.*, 868 F.2d 1226, 1236, 9 USPQ 2d 1913, 1920 (Fed. Cir. 1989). To constitute anticipation, the claimed subject matter must be identically disclosed in the prior art. *In re Arkley*, 172 U.S.P.Q. 524 at 526 (C.C.P.A. 1972). For anticipation, there must be no difference between the claimed invention and the reference disclosure, as viewed by a person of ordinary skill in the art. *Scripps Clinic & Res. Found. v. Genentech, Inc.*, 927 F.2d 1565, 18 USPQ2d 101 (Fed. Cir. 1991). To overcome the defense of anticipation, "it is only necessary for the patentee to show some tangible difference between the invention and the prior art." *Del Mar Engineering Lab v. Physio-Tronics, Inc.*, 642 F.2d 1167, 1172, (9th Cir. 1981).

Moreover, an anticipation rejection that is based on inherency must be supported by factual and technical grounds establishing that the inherent feature must flow as a necessary conclusion, not simply a possible conclusion, from the teaching of the cited art. *Ex parte Levy*, 17 U.S.P.Q.2d 1461, 1464 (Bd. Pat. App. & Int. 1990); *In re Oelrich*, 666 F.2d 578, 212 U.S.P.Q. 323, 326 (C.C.P.A. 1981).

Claim 2 is directed to a method of presenting an *antigenic peptide* on the surface of a viable cancer cell, said method comprising: contacting said cancer cell with said antigenic peptide and with a photosensitizing agent, wherein said peptide and said agent are each taken up into an intracellular membrane-restricted compartment of said cell; irradiating said cell with light of a wavelength effective to activate the photosensitizing agent, such that the membrane of said intracellular compartment is disrupted, releasing said peptide into the cytosol of the cell, without killing the cell; wherein, said released antigenic peptide, or a part thereof of sufficient size to generate a cytotoxic T cell

response, is subsequently presented on the surface of said cell by a class I MHC molecule; wherein presentation of the antigenic peptide, or part thereof, on the surface of said cell results in cytotoxic T cell mediated cell killing; and wherein the photosensitizing agent is selected from the group consisting of a porphyrin, phthalocyanine and a chlorin.

Claim 24 is directed to a method of presenting an *antigenic peptide* or a part thereof on the surface of a viable antigen presenting cell, said method comprising: contacting said cell with the antigenic peptide and with a photosensitizing agent, wherein said peptide and said agent are each taken up into an intracellular membrane-restricted compartment of said cell; irradiating said cell with light of a wavelength effective to activate the photosensitizing agent, such that the membrane of said intracellular compartment is disrupted, releasing said peptide into the cytosol of the cell, without killing the cell; wherein, said released peptide, or a part thereof of sufficient size to generate an immune response, is subsequently presented on the surface of said cell by a class I or II MHC molecule; wherein presentation of the peptide, or part thereof, on the surface of said cell results in stimulation of an immune response; and wherein the photosensitizing agent is selected from the group consisting of a meso-tetraphenylporphine with 4 sulfonate groups ($TPPS_4$), meso-tetraphenylporphine with 2 sulfonate groups on adjacent phenyl rings ($TPPS_{2a}$), or aluminum phthalocyanine with 2 sulfonate groups on adjacent phenyl rings ($AlPcS_{2a}$).

WO96/07432 is limited to delivery of *active, whole molecules* to the *cytosol* of cells. In contrast, the present invention is directed to a method of presenting an *antigenic peptide* on the *surface* of a *viable* cancer cell or antigen presenting cell. While the Examiner alleges that practice of the methods of WO96/07432 inherently leads to presentation of antigenic peptides on cells, the evidence provided in WO96/07432 shows the opposite. Thus, WO96/07432 explicitly discloses and teaches that whole, large molecules internalized by the methods described therein will be intact and remain in the cytosol. Hence, the Examiner inherency argument fails for lack of evidence, and for a teaching that explicitly shows the opposite.

The fact that the WO96/07432 methods explicitly lead to internalization of whole, intact molecules is demonstrated as follows. Each of Figures 2, 4-12 and 13 of

WO96/07432 shows the amount of protein synthesis that occurs in cells after whole, active molecules of protein translation inhibitors (gelonin, saporin and agrostin) are transported into the cytosol. In each case, such transportation gives rise to about 100-fold less protein translation. Such results prove that the protein translation inhibitors were *intact*, *whole* molecules that were *functionally active* and therefore interact with and modulate the translation apparatus of the cell. No other interpretation of the WO96/07432 data is possible.

Moreover, as shown in FIG. 3 of the WO96/07432 disclosure, when gelonin is transported into the cytosol through exposure to light, the cells essentially *all die* after 50 to 100 seconds of light exposure. Accordingly, *no antigen presentation* occurs when the methods of WO96/07432 are practiced.

Claim 2 requires that the following somewhat abbreviated steps be performed:

i) a cancer cell is contacted with an antigenic peptide and a photosensitizing agent which are taken up into the cell;

ii) the cell is irradiated to activate the photosensitizing agent, the peptide is released into the cytosol without killing the cell;

iii) the peptide (or a part thereof) is presented on the cell surface by class I MHC molecules;

iv) cytotoxic T cell mediated cell killing results.

As explained in more detail below, WO96/07432 does not disclose methods that include steps (i) and (ii). Therefore, steps (iii) and (iv) cannot occur when the WO96/07432 procedures are employed.

The Examiner has pointed to WO96/07432 Figure 2 as allegedly teaching the invention. Thus, for the purposes of illustration, the experiment whose results are presented in that Figure will be considered. WO96/07432 Figure 2 presents the results of experiments described in Example 1. In that case the plant toxin gelonin was used. As set forth on page 8, lines 13-15 of WO96/07432, gelonin is a plant toxin that inhibits protein synthesis in cell-free systems but has little or no effect on intact cells. NHIK3025 cells were incubated with gelonin with or without $TPPS_{2a}$ and/or light as set forth in the description of Figure 2 (see page 3). The curve with open circles in Figure 2 illustrates

the effects of contacting the cell with gelonin and the photosensitizing agent, then irradiating this mixture. As shown, the relative protein synthesis of the cells exposed to gelonin and light drops dramatically as the amount of gelonin increases. As noted in the Example on page 8 at lines 23-24, "protein synthesis can be completely inhibited by combining PDT and gelonin." Therefore, this procedure resulted in cell death.

Claim 2 requires that the antigenic peptide is taken up into the cell (step (i) above). However, in Example 2 of WO96/07432, when this occurs the cell dies. Step (ii) of Applicant's claim 2 requires that the cell is not killed. Thus the methods of WO96/07432 do not disclose Applicant's step (ii). Furthermore, because cell death has occurred, gelonin could not be presented on the cell surface. Thus the method fails to achieve step (iii) of claim 2. Finally, no CTL mediated cell killing can occur, firstly because no cell surface presentation has occurred and secondly because no CTLs are present in the experiment that has been conducted.

Thus there are two possible outcomes for cells treated according to Example 1 of WO96/07432. The first is that gelonin is internalized by the PDT method. In that case the gelonin will exert its toxic effect on the cell and cell death will result. Cell surface presentation of gelonin or a part thereof is hence not possible. The second alternative is that the gelonin is not internalized, e.g. the cell fails to take up gelonin because the cell is contacted with insufficient gelonin or the PDT method is not effective. In that case no cell death from gelonin will result, but gelonin will not have been internalised and hence no cell surface presentation of that molecule or a part thereof is possible. As noted above, in the methods which are described in WO96/07432 essentially all cells are killed and thus the first outcome, i.e. gelonin uptake and hence cell death, predominates.

The other examples in WO98/07432 are all concerned with the use of toxins which have similar effects, namely saporin and agrostin, and again either the toxins are not internalized or if internalized cause cell death. Thus, the methods of WO98/07432 do not disclose or teach Applicant's methods because these methods invariably lead to cell death.

Thus, WO96/07432 fails to disclose at least the following elements of Applicant's invention:

i) the cell is irradiated to activate the photosensitizing agent, the peptide is released into the cytosol without killing the cell;

ii) the peptide (or a part thereof) is presented on the cell surface by class I MHC molecules;

iii) cytotoxic T cell mediated cell killing results.

Therefore, no anticipation can be found because the claims explicitly set forth steps not disclosed by WO96/07432, and no factual and technical grounds exist establishing that the inherent feature must flow as a necessary conclusion, not simply a possible conclusion, from the teaching of the cited art. *Ex parte Levy*, 17 U.S.P.Q.2d 1461, 1464 (Bd. Pat. App. & Int. 1990); *In re Oelrich*, 666 F.2d 578, 212 U.S.P.Q. 323, 326 (C.C.P.A. 1981). Here, all evidence and data of record clearly shows that the methods disclosed by WO96/07432 yield results opposite to those claimed by Applicant. In particular, WO96/07432 yields dead cells where Applicant's claim live cells, WO96/07432 yields cells with whole molecules in their cytosol where Applicant's claim cells that display peptides on their cell surface. Finally, the WO96/07432 disclosure would not lead one of skill in the art to expect CTL mediated cell killing to occur, firstly because no cell surface presentation has occurred and secondly because no CTLs are present or contemplated by the WO96/07432 disclosure.

Accordingly, WO96/07432 neither explicitly nor inherently anticipates the subject matter of the claimed invention. Applicant requests withdrawal of this rejection of claims 2, 4, 6, 8-10 and 22 under 35 U.S.C. § 102(b).

Conclusion

Applicants respectfully submit that the claims are in condition for allowance, and notification to that effect is earnestly requested. The Examiner is invited to telephone Applicants' attorney at (516) 795-6820 to facilitate prosecution of this application.

If necessary, please charge any additional fees or credit overpayment to Deposit Account No. 19-0743.

Respectfully submitted,

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CERTIFICATE UNDER 37 CFR 1.8: The undersigned hereby certifies that this correspondence is being deposited with the United States Postal Service with sufficient postage as first class mail, in an envelope addressed to: MS Amendment, Commissioner of Patents, P.O. Box 1450, Alexandria, VA 22313-1450, on this 30th day of October, 2007.

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